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Human Y-chromosome: a hall of mirrors

The human Y-chromosome is back in the news. This time with a different message suggesting that the chromosome has been evolving a very interesting, unexpected adaptive strategy that can effectively counter the forces leading to sequence loss. Y-chromosome biologists who have been studying its sequence evolution argued that the mammalian XY pair arose from autosomes some few hundred million years ago (Waters *et al* 2001; Graves 1995). This was followed by a suppression of recombination almost all along the length, except at the very tips (pseudoautosomal regions) of the chromosomal pair. This crucial molecular event robbed the Y-chromosome of the possibility of homology based repair, while the X-chromosome retained it at least 50% of the time, i.e. in XX females. This resulted in a "repeat-rich/gene-poor/decaying wreck-land" Y-chromosome that has now shrunk to the smallest of all chromosomes, and may even vanish completely in the next 5–10 million years (Graves 1995, 2002). Its doomsday has been discussed by Trounson (1999). But it seems that the verdict was rather premature and inaccurate. This is demonstrated by two papers by David C Page and his colleagues (Rozen *et al* 2003; Skaletsky *et al* 2003). Their findings, as described below, are revealing.

They sequenced the euchromatic part of the Y-chromosome (23 Mb) (obtained from a single anonymous human male), comprising 8 Mb of the short arm (Yp) and 14·5 Mb of the long arm (Yq), at an accuracy of 99·999% and classified these regions into three sequence categories: (i) a 3·4 Mb stretch, recently (less than 5 million years ago) transposed from the X-chromosome, housing 2 single copy genes; (ii) an ancient 8·6 Mb stretch (50–300 million year old) that houses decaying relics of autosomal sequences, encompassing 16 ubiquitously expressing genes; and (iii) a 10·2 Mb stretch, acquired and amplified (hence referred as "ampliconic") from autosomes during the last 50–300 million years, housing essentially all testis-specific genes, the most important category for maintaining the phenotype of maleness. Careful analyses of repeat sequence organization revealed that all the testes-specific genes in the third category were present as two copies each, facing each other as mirror images and separated by spacers of varying length in a total of eight palindromes. The high level of accuracy achieved in sequencing enabled them to demonstrate that the two mirror-image arms of each palindrome set were highly sequence-related, with a sequence divergence as low as 0·01%. Interestingly, the study revealed a similar "invert repeat" organization for all essential testes specific genes in the "ampliconic" region of chimpanzee Y-chromosome as well. Again, an extremely high level of sequencing quality led to the conclusion that two palindromic arms of chimpanzee gene-pair had (as in the human-Y ampliconic region) very low (0·01%–0·02%) sequence divergence. On the other hand, expectedly, the interspecies divergence (human vis-à-vis their orthologous gene-pairs in chimpanzee) was significantly higher (1·4%–2·3%). The implication would be that for the last 5 million years, following the separation of human and chimpanzee lineages, these sequences have been diverging at a normal rate. But the sequences have been "homogenised" within a species, a hall-mark of a classical "gene conversion" process. In other words, mutations that occurred in one copy of the gene-pair were corrected by gene-conversion as quickly as they arose by a molecular cross-talk between the two arms of the palindromes within the species. A simple back calculation that would account for as low as 0·01%–0·02% sequence divergence, almost completely nullifying a normal rate of mutational pressure in the mirror-repeat genes, suggested that on an average "600 nucleotides must have undergone arm-to-arm gene conversion for each new born male" in the human population, a feverish level of gene-conversion activity. Is there a directionality to such gene-conversions such that deleterious mutations are selectively rejected? The answer is far from clear, although current molecular genetic data on meiotic as well as mitotic gene conversions in eucaryotic genomes strongly hint at clear bias of gene conversions towards GC-pairs (Marais 2003). It has been argued that mutations produce more AT than GC-pairs and the intrinsic bias in gene-conversion towards GC-pairs can substantially reduce the

mutation load, even if the conversion bias and rate are weak (Galtier *et al* 2001; Bengtsson 1990). However, quantitative predictions from such models are difficult to make owing to the non-equilibrium status of the genome.

Is the proposed rescue mechanism of gene conversion merely intelligent speculation, or is it really happening in this region? The authors actually capture gene conversion "in its act" by an uncanny method. They argue that if the proposal is true and the conversions are as frequent as purported, one should be able to obtain a "steady state snap-shot" of the process by specifically screening for sequence changes associated with mirror-repeats in samples representing the entire human Y-chromosome geneology tree (Cavali-Sforza and Feldman 2003). In fact, they do. They sequenced two CDY genes in 171 men, representing all 42 branches of the Y-geneology tree and recovered a C-nucleotide at the same site on both arms of the palindrome (CC-configuration) as well as equivalent CT and TT configurations, the former confining to about 37 branches, while the latter two to a young cluster of five closely-related branches. This revealed that a C to T transition was the origin of such a change, where TT configuration represented the "act" of gene conversion from that of CT.

In summary, a strong case has been made for saying that testes-specific genes in the ampliconic region of a single Y-chromosome now enjoy the "diploidy status" that rivals two autosomal homologues, an organization that can effectively beat the drawbacks of an otherwise non-recombining Y-chromosome. It appears that about 5 million years ago, Y-chromosome evolution took an adaptive strategy that, relying on the ampliconic nature of its male-specific sequences, "mirror imaged" the genes and began recombining one with the other intrachromosomally. Thus the so called non-recombining Y (NRY) has now been more appropriately termed as the male-specific-Y (MSY). This should allay fears of its disappearance.

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